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The Effects of Phosphodiesterase-5 Inhibition With Sildenafil on Pulmonary Hemodynamics and Diffusion Capacity, Exercise Ventilatory Efficiency, and Oxygen Uptake Kinetics in Chronic Heart Failure

Marco Guazzi, MD, PHD, FACC,* Gabriele Tumminello, MD,* Fabio Di Marco, MD,† Cesare Fiorentini, MD,* Maurizio D. Guazzi, MD, PHD‡

Milan, Italy

OBJECTIVES We sought to investigate the effects of sildenafil, a phosphodiesterase-5 (PDE_5) inhibitor, on lung function and exercise performance in chronic heart failure (CHF).

BACKGROUND In CHF, nitric oxide-mediated regulation of lung vascular tone and alveolar-capillary membrane conductance is impaired and contributes to exercise intolerance. The potential for benefits due to increased nitric-oxide availability is unexplored.

METHODS In 16 patients with CHF and 8 normal subjects, we measured—before and 60 min after sildenafil (50 mg) or placebo—ejection fraction, pulmonary hemodynamics, carbon monoxide diffusion capacity (DLco), with its membrane (D_M) and capillary blood volume (V_c) subcomponents, endothelial function (brachial reactive hyperemia) at rest, peak oxygen uptake (VO_2), increments in VO_2 versus work rate ($\Delta VO_2/\Delta WR$), changes in ventilation versus CO_2 production (VE/VCO_2) slope, and recovery VO_2 time constant (tau) on exertion.

RESULTS In CHF, sildenafil did not affect cardiac index, wedge pulmonary pressure, or ejection fraction; it significantly ($p < 0.01$) decreased pulmonary mean artery pressure (−20.4%) and arteriolar resistance (−45.1%), VE/VCO_2 slope (−9.0%) and recovery tau (−25.8%), and increased ($p < 0.01$) DLco (+11.1%), D_M (+9.9%) peak VO_2 (+19.7%), $\Delta VO_2/\Delta WR$ (+11.0%), and brachial reactive hyperemia (+33.3%). No variations occurred in normal subjects and after placebo. Changes in DLco were related to those in VE/VCO_2 slope ($r = -0.71$; $p = 0.002$), and changes in brachial hyperemia correlated with those in $\Delta VO_2/\Delta WR$ ($r = 0.80$; $p = 0.0002$).

CONCLUSIONS This study shows that in CHF PDE_5 inhibition modulates pulmonary pressure and vascular tone, and improves DLco, exercise peak VO_2, aerobic ($\Delta VO_2/\Delta WR$) and ventilatory (VE/VCO_2 slope) efficiencies, and oxygen debt (recovery tau). Endothelial mechanisms may underlie these effects. (J Am Coll Cardiol 2004;44:2339–48) © 2004 by the American College of Cardiology Foundation

Nitric oxide secretion by the pulmonary arterial and venous endothelia plays an important role in lung physiology (1) because it is involved in the special capacity of the vasculature to adapt to local changes in blood flow, in maintenance of normal pulmonary vascular tone and permeability (2), and in the modulation of the tissue component of resistance to O_2 transfer from the alveolus to its uptake by hemoglobin (3).

At the lung level, chronic heart failure (CHF) is typically associated with secondary hypertension, impaired vascular reactivity and permeability, and reduced alveolar-capillary membrane conductance (D_M) (4). These factors contribute to dyspnea sensation and exercise intolerance (5,6). The question we have attempted to answer is whether a defective nitric oxide release disturbs the lung physiology in patients with CHF, as it does in patients with primary pulmonary hypertension (7), and whether a greater nitric oxide availability can be beneficial.

Sildenafil was used to investigate these issues because: 1) it is a selective inhibitor of cyclic 3′-5′-guanosine monophosphate-specific phosphodiesterase-5 (PDE_5), the predominant isoenzyme that metabolizes cyclic 3′-5′-guanosine monophosphate, the second messenger of nitric oxide (8); 2) the gene encoding PDE_5 is highly expressed in the lung (9); 3) PDE_5 inhibitors have a promising therapeutic potential in pulmonary hypertension (10); 4) agonist-induced and shear stress-induced nitric oxide-mediated vasodilation are decreased in skeletal muscle circulation of patients with CHF (11); and 5) acute PDE_5 inhibition with sildenafil increases flow-mediated vasodilation in CHF (12).

METHODS

Patients and normal subjects. The study includes 16 male patients referred for evaluation of CHF and 8 healthy men of similar age with atypical chest pain and normal coronary angiography and without any drug prescription. Patients were in stable clinical condition (New York Heart Associ-

From the *Cardiopulmonary Laboratory, Cardiology Division, University of Milano, San Paolo Hospital, Milan, Italy; †Respiratory Unit, University of Milano, San Paolo Hospital, Milan, Italy; and ‡Institute of Cardiology, University of Milano, Milan, Italy. Supported, in part, by a grant from the Luigi Berlusconi Foundation, Milano, Italy. Presented, in part, at the 76th American Heart Association Scientific Sessions, Orlando, Florida, November 9 to 12, 2003.

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Abbreviations and Acronyms

AT	= anaerobic threshold
CHF	= chronic heart failure
CPET	= cardiopulmonary exercise testing
DLco	= lung diffusing capacity for carbon monoxide
D_M	= alveolar-capillary membrane conductance
PDE_5	= phosphodiesterase-5
tau	= oxygen uptake time constant
V_A	= alveolar volume
V_c	= pulmonary capillary blood volume
VCO_2	= carbon dioxide output
VE/VCO_2 slope	= slope of increase in ventilation versus carbon dioxide output
VO_2	= oxygen uptake
$\Delta VO_2/\Delta WR$	= rate of oxygen uptake increase per work rate

ation functional class II to III), and CHF was due to ischemic or idiopathic cardiomyopathy. Eligibility criteria were: consent to participate in the study after information concerning procedures, risks, and possible clinical benefits; left ventricular ejection fraction ≤40%; forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio >70%; and ability to complete a maximal exercise test. Patients were excluded if they had hypertension, pulmonary disease, a pack-years index of cigarette smoking of more than 10 (all had abstained from tobacco products for at least 8 months [13] before enrollment); if their carboxyhemoglobin was >2%; if exercise was limited by symptoms other than dyspnea or fatigue and they developed electrocardiographic changes of myocardial ischemia during exertion. The anti-failure treatment was that prescribed by the referring physician and included diuretics (in all), angiotensin-converting enzyme inhibitors (14 patients), beta-blockers (11 patients), and aspirin (10 patients). We considered these patients as representative of the CHF population. The experimental protocol was performed as approved by the local ethics committee. All subjects gave written consent to the procedures, and none were excluded after study inclusion.

Hemodynamics. For cardiac output and pulmonary pressure measurements, a 5-F thermodilution double-lumen balloon-tipped catheter was inserted into an autecubital vein and positioned in the pulmonary artery. Systemic vascular resistance (SVR) and pulmonary arteriolar resistance (PAR) were calculated as follows:

$$SVR = MAP - MRAP \times 1,332 \times 60 / CO$$
$$PAR = MPP - MWPP \times 1,332 \times 60 / CO$$

where MAP = mean systemic arterial pressure, MRAP = mean right atrial pressure, MPP = mean pulmonary arterial pressure, MWPP = mean pulmonary wedge pressure, and CO = cardiac output. Left ventricular dimensions and volumes and mitral regurgitation were quantitated with two-dimensional and Doppler echocardiography. These measurements were obtained at rest.

Table 1. Baseline Characteristics of Study Subjects

	Normal Subjects	Patients
Number	8	16
Gender (M/F)	8/0	16/0
Age (yrs)	57.6 ± 7.2	55.1 ± 8.2
Weight (kg)	76.3 ± 5.4	74.7 ± 6.6
Body mass index	26 ± 3	25 ± 2
Etiology of heart failure (IHD/DCM)	—	11/5
Mitral regurgitation (subjective scale, 0–4)	—	1.3 ± 0.7
Forced vital capacity (% predicted)	96.3 ± 10.1	91.6 ± 7.8
Forced expiratory volume in 1 s (% predicted)	97.6 ± 11.0	87.8 ± 8.7*
DLco (% predicted)	99.2 ± 7.1	75.9 ± 9.9*
$DLco/V_A$ (% predicted)	97.8 ± 8.3	75.4 ± 12.6*
Cardiac index ($l \cdot min^{-1} \cdot m^2$)	3.127 ± 112	2.234 ± 127*
Left ventricular ejection fraction (%)	68.2 ± 5.4	30.2 ± 3.2*
Systemic arterial pressure (mm Hg)		
Systolic	128.5 ± 5.2	121.1 ± 6.8
Diastolic	79.6 ± 2.3	74.8 ± 1.5
Pulmonary arterial pressure (mm Hg)		
Systolic	23.5 ± 4.2	33.6 ± 3.3*
Diastolic	12.8 ± 3.7	21.5 ± 2.7*
Wedge	11.9 ± 2.8	18.9 ± 3.1*
Systemic vascular resistance ($dynes \cdot s \cdot cm^{-5}$)	1,236 ± 188	1,938 ± 136*
Pulmonary arteriolar resistance ($dynes \cdot s \cdot cm^{-5}$)	76 ± 17	129 ± 18*

*$p < 0.01$ vs. normal subjects.
DCM = idiopathic dilated cardiomyopathy; DLco = lung diffusing capacity for carbon monoxide; IHD = ischemic heart disease; V_A = alveolar volume.

Pulmonary function tests. Spirometry was performed with equipment that met the American Thoracic Society performance criteria (13). To adjust for height, age, and gender we used prediction equations for FEV_1 and FVC (14).

Diffusing lung capacity for carbon monoxide (DLco) was determined twice with washout intervals of at least 4 min (the average was taken as the final result) with a standard single breath technique. A test gas was used with 0.28% carbon monoxide, 0.30% methane, 21% oxygen (O_2), and the balance made up of nitrogen. The D_M and the capillary pulmonary blood volume available for gas exchange (V_c) were determined with the classic method of Roughton and Forster (15). The single-breath alveolar volume (V_A) was derived by methane dilution.

Cardiopulmonary exercise testing (CPET). Subjects performed a standard, progressively increasing (personalized ramp protocol) work rate (WR) CPET to maximum tolerance on a cycle ergometer in the upright position. Gas exchange measurements (Cardiopulmonary Metabolic Cart, Sensormedics Vmax Spectra, Sensormedics, Yorba Lima, California) were obtained at rest (2 min) and during 2 min of unloaded leg cycling at 60 rpm, followed by a progressively increasing WR exercise. Heart rate, 12-lead electrocardiogram, and cuff blood pressure were monitored and recorded.

Minute ventilation (VE), oxygen uptake (VO_2), carbon

Table 2. Hemodynamic Values at Baseline and After Sildenafil (50 mg) or Placebo Intake in Normal Subjects and in Patients with CHF (means ± SD)

	Normal Subjects						CHF Patients					
	Baseline	Placebo	Δ	Baseline	Sildenafil	Δ	Baseline	Placebo	Δ	Baseline	Sildenafil	Δ
Subjects (n)	8	8		8	8		16	16		16	16	
Heart rate (beats/min)	66.1 ± 2.7	67.8 ± 2.8	+1.7	66.5 ± 2.6	68.0 ± 2.6	+1.5	72.3 ± 2.8	71.9 ± 2.7	−0.4	71.4 ± 2.4	71.0 ± 7.7	−0.4
Systemic arterial pressure (mm Hg)												
Systolic	125.4 ± 4.2	126.5 ± 3.8	+1.1	127.2 ± 4.2	125.7 ± 5.2	−1.5	120.3 ± 6.7	121.0 ± 6.8	+0.7	121.4 ± 6.4	115.6 ± 9.0	−5.8
Diastolic	77.5 ± 3.8	79.4 ± 2.6	+1.9	78.3 ± 2.3	78.2 ± 3.1	−0.1	74.7 ± 2.8	74.6 ± 5.7	−0.1	75.3 ± 3.2	73.7 ± 5.6	−1.6
Cardiac index ($l \cdot min^{-1} \cdot m^2$)	3.247 ± 131	3.180 ± 13.0	−0.067	3.209 ± 118	3.259 ± 129	+0.050	2.271 ± 132	2.231 ± 138	−0.040	2.211 ± 130	2.345 ± 138	+0.134
Systemic vascular resistance ($dynes \cdot s \cdot cm^{-5}$)	1,210 ± 166	1,256 ± 162	+46	1,225 ± 162	1,200 ± 152	−25	1,935 ± 149	1,950 ± 135	−15	1,895 ± 149	1,805 ± 153	−90
Left ventricular ejection fraction (%)	66.7 ± 3.3	67.7 ± 3.4	+1	67.3 ± 4.3	66.2 ± 4.0	−1.1	30.2 ± 3.1	31.6 ± 2.8	+1.4	30.8 ± 3.0	32.9 ± 2.6	+2.1
Pulmonary arterial pressure (mm Hg)												
Systolic	24.0 ± 3.7	24.1 ± 3.9	+0.1	23.5 ± 4.1	23.7 ± 4.0	+0.2	33.7 ± 3.2	33.5 ± 2.9	−0.2	32.9 ± 2.7	25.7 ± 3.1*†	−7.2†
Diastolic	12.6 ± 3.1	12.3 ± 3.5	−0.3	12.6 ± 3.2	12.1 ± 3.9	−0.5	22.2 ± 2.5	22.1 ± 2.7	−0.1	22.2 ± 2.6	17.6 ± 2.7*†	−4.6†
Wedge pulmonary pressure (mm Hg)	11.1 ± 2.2	10.7 ± 2.5	−0.4	10.7 ± 3.3	10.2 ± 3.6	−0.5	19.4 ± 2.7	19.6 ± 2.3	+0.2	18.5 ± 3.0	17.3 ± 2.7	−1.2
Pulmonary arteriolar resistance ($dynes \cdot s \cdot cm^{-5}$)	71 ± 26	75 ± 29	+4.0	74 ± 20	76 ± 23	+2.0	129 ± 16	131 ± 16	+2.0	127 ± 17	57 ± 15*†	−70†

*$p < 0.01$ vs. baseline; †$p < 0.01$ vs. placebo.
CHF = chronic heart failure. Δ = changes from baseline.

dioxide output (VCO_2), and other exercise variables were computer-calculated breath-by-breath, interpolated second-by-second, and averaged at 10-s intervals. The V-slope analysis method was used to measure the anaerobic threshold (AT).

The VO_2 at the AT and the rate at which VO_2 increased per work rate ($\Delta VO_2/\Delta WR$), as an indicator of aerobic efficiency, were also assessed. The $\Delta VO_2/\Delta WR$ was calculated using all VO_2 data for the progressively increasing exercise period beginning 1 min after WR started to increase until peak exercise. According to what has recently been proposed by Mitchell et al. (16), we measured the VO_2 kinetics during exercise using the last minute of unloaded pedaling (to determine delay of increase in VO_2 before and with the start of exercise) and the $\Delta VO_2/\Delta WR$ alone that was measured by linear regression analysis, taking into account the inflection point at AT. We also recorded the kinetics for the first 6 min after peak exercise to allow for determination of recovery time constant for VO_2 (tau). Tau calculation was performed by fitting the VO_2 data to a monoesponential curve $(VO_2 = Ae^{B[\tau - TD]} + C)$.

Peak VO_2 was the highest VO_2 achieved during exercise. The O_2 arterial saturation was monitored with an ear oxymeter (Sensormedics).

Vascular studies. Imaging studies of the brachial artery were performed with a high-resolution ultrasound Hewlett-Packard 11 MHz linear-array transducer (Palo Alto, California). Brachial flow velocity was assessed by pulsed Doppler with the range gate (1.5 mm) in the center of the artery. The system permitted an evaluation of the angle between blood stream and the intersecting ultrasound beam, which was used to calculate blood flow velocity. Images were obtained by the same investigator throughout the study. Flow-mediated vasodilation was measured as change in brachial artery diameter during hyperemia after release of a cuff inflated (50 mm Hg above systolic pressure for 5 min) on the forearm. Diameter was measured in millimeters, coincident with the R waves on the electrocardiogram, at two sites along the artery for three cardiac cycles, with these six measurements averaged. Images and vasodilating responses from repeated studies were analyzed by an investigator blind to the sequence.

We calculated blood flow, multiplying the velocity-time integral of the Doppler flow signal by the vessel cross-sectional area and heart rate. The flow-mediated dilation was calculated as absolute maximal change in diameter (30 s after cuff deflation) compared with baseline. Reactive hyperemia was calculated as absolute maximal change in flow during hyperemia compared with baseline.

Sources of variability were studied for measurement of brachial artery diameter (BAD) and flow-mediated dilation (FMD) in the control condition (C) and after sildenafil (S). For reproducibility, coefficients of variations were: BADC = 2.3, BADS = 2.5, FMDC = 3.1, FMDS = 2.8. For repeatability, coefficients of variation were: BADC = 2.7, BADS = 2.5, FMDC = 2.9, FMDS = 3.0.

Protocol. Subjects were hospital admitted. Patients were maintained on their current drug therapy, and control subjects did not receive any cardiovascular treatment. After routine laboratory work and cardiac evaluation, they performed a graded CPET to determine peak VO_2. Then subjects underwent pulmonary evaluation, including diffusion capacity, and these measurements were taken as baseline parameters, as far as the lung function is concerned (day 1). On the following day (day 2), drug studies were performed in all participants after a 12-h overnight fast in a quiet room. Patients' morning doses of their usual medications were withheld. A second CPET was performed, and results were taken as baseline measurements. A 5-F thermodilution balloon-tipped catheter was floated to the pulmonary circulation. After a 30-min rest, diameter and flow of the brachial artery were measured before cuff inflation. A second scan was taken for 90 s after cuff deflation with measurements taken 15, 30, 60, and 90 s after deflation. After an additional 30-min rest, baseline blood pressure (cuff method), right atrial pressure (proximal port of the catheter), pulmonary arterial and wedge pressures, and cardiac output (average of three determinations) were evaluated. Then 50 mg of sildenafil or placebo were administered orally. The criteria for selection of a 50-mg dose was that of utilizing the minimal dose that, in a pilot assay in five similar patients, significantly reduced the pulmonary arteriolar resistance.

Sixty minutes later (to coincide with the expected peak plasma concentration after oral dosing [8]), hemodynamics, pulmonary function, and brachial flow-mediated vasodilation were reevaluated in that order, at rest. Then, according to the indications of the ethics committee, the catheter was withdrawn and a CPET was repeated. Measurements were not made at other times after dosing in order to allow at least 24-h before reassessing DLco and its subcomponents. On the following morning (day 3), we repeated the same procedures as on day 2, while patients were switched to placebo or sildenafil according to a random double-blind crossover design.

Statistical analysis. Randomization was performed according to a randomization list generated by computer. Values are expressed as the mean values ± SD. Repeated measures analysis of variance test and Newman-Keuls multiple comparison procedure were used to compare measurements after placebo and after sildenafil intake. The incremental changes from baseline with active drug compared with placebo were analyzed with a paired *t* test.

Differences between control subjects and patients were analyzed by an unpaired *t* test. The relationships of changes in DLco versus those in VE/VCO_2 slope and changes in brachial reactive hyperemia versus those in $\Delta VO_2/\Delta WR$, as well as those between tau recovery versus brachial reactive hyperemia and $\Delta VO_2/\Delta WR$, were assessed using the Pearson coefficient of correlation. A p value of <0.05 was

considered significant. Statistical analyses were performed by means of the Stata 7.0 package (Stata Corp. LP, College Station, Texas).

RESULTS

None of the patients or normal subjects was withdrawn for major adverse events. The two populations were similar as to gender, age, and body mass index (Table 1). In patients, DLco and DLco/V_A were reduced to 75.9% and 75.4% of predicted normal values, respectively; FEV_1 and FVC were 87.8% and 91.6% (Table 1). Compared with healthy subjects, left ventricular ejection fraction and cardiac index were reduced; systolic, diastolic, and wedge pulmonary pressures and pulmonary arteriolar resistance were elevated (Tables 1 and 2). As to the CPET parameters (Table 3), patients exhibited significant lower peak VO_2, VO_2 at AT, and higher dead-space-to-tidal-volume ratio (VD/VT) and VE/VCO_2 slope. No significant differences in VO_2 time delay were observed. The $\Delta VO_2/\Delta WR$, which reflects the O_2 utilized per unit increase in WR and is an index of aerobic efficiency, averaged 8.0 ± 1.9 $ml \cdot W^{-1} \cdot min^{-1}$, compared with 10.6 ± 3.0 $ml \cdot W^{-1} \cdot min^{-1}$ in normal controls. The recovery tau in patients (76.7 ± 14.0 s) exceeded that in healthy subjects by 42% (44.0 ± 16.0 s).

Flow-mediated changes in brachial artery diameter and reactive hyperemia were significantly smaller in patients than in normal individuals (Table 4).

Variations from baseline (with placebo or sildenafil) in hemodynamic, CPET, brachial artery, and pulmonary function data are reported in Tables 2 to 5, respectively. Because there was no time or order effect, data are presented regardless of the order in which placebo and sildenafil were given. In healthy subjects, after a 60-min interval following placebo or sildenafil, the hemodynamic, CPET, respiratory, and vascular variables all were similar to those detected at baseline. No significant variations with placebo were observed in patients with CHF. On the contrary, measurements performed after sildenafil in this group showed a reduction in pulmonary systolic (−21.8%) and diastolic (−20.7%) arterial pressures and arteriolar resistance (−45.1%), without significant changes in cardiac index (+6.0%) and wedge pulmonary pressure (−6.4%) (Table 2). There was an increase in DLco (+11.1%) and D_M (+9.9%) (Table 5). Sildenafil improved DLco and D_M in all but one patient. These variations, when expressed per unit V_A, were: DLco/V_A +20%, D_M/V_A +19%. Arterial O_2 saturation in either population was normal both at baseline and during peak exercise, and did not vary after sildenafil (Table 5). The forearm reactive hyperemia and flow-mediated dilation were significantly augmented after PDE_5 inhibition (Table 4).

As shown in Table 3, sildenafil was associated with significant decrease in VD/VT (−13.6%) and VE/VCO_2 slope (−9.0%), and increase of exercise workload at AT (+14.1%) and at peak exercise (+11.0%), peak VO_2 (+19.7%), VO_2 at AT (+20.6%), and $\Delta VO_2/\Delta WR$ (+11.0%). The $\Delta VO_2/$

Table 3. CPET Data at Baseline and After Placebo or Sildenafil Intake in Normal Subjects and in Patients with CHF (Mean ± SD)

	Normal Subjects						CHF Patients					
	Baseline	Sildenafil	Δ	Baseline	Placebo	Δ	Baseline	Placebo	Δ	Baseline	Sildenafil	Δ
Subjects (n)	8	8		8	8		16	16		16	16	
VO_2 time delay (s)	83.2 ± 9.9	84.6 ± 10.7	+1.4	83.6 ± 9.6	83.5 ± 9.7	−0.1	86.2 ± 10.7	87.2 ± 11.1	+1.0	87.1 ± 9.9	88.1 ± 10.1	+1.0
Workload AT (W)	104.3 ± 22.9	104.4 ± 23.7	+0.1	102.9 ± 29.6	104.9 ± 23.3	+2.0	66.7 ± 26.1	67.5 ± 27.2	+0.8	65.8 ± 26.7	75.1 ± 28.3*†	+9.3†
VO_2 AT ($ml \cdot min^{-1} \cdot kg^{-1}$)	16.9 ± 4.0	16.9 ± 4.2	0	16.2 ± 4.1	16.6 ± 4.0	+0.4	8.9 ± 4.05	9.2 ± 4.1	+0.3	8.8 ± 3.3	11.5 ± 3.9*†	+2.7†
Peak workload (W)	155.8 ± 41.5	156.3 ± 43.2	+0.5	154.4 ± 27.8	156.4 ± 26.2	+2.0	101.2 ± 29	99.8 ± 30.0	−1.4	100.1 ± 29	111.2 ± 2.7*†	+11.1†
Peak VO_2 ($ml \cdot min^{-1} \cdot kg^{-1}$)	24.8 ± 4.6	24.9 ± 2.6	+0.1	24.7 ± 4.2	24.6 ± 5.1	−0.1	15.9 ± 3.1	16.2 ± 3.2	+0.3	16.2 ± 2.8	19.4 ± 3.0*†	+3.2†
Peak RER	1.18 ± 0.08	1.17 ± 0.07	−0.01	1.18 ± 0.07	1.16 ± 0.09	−0.02	1.15 ± 0.09	1.14 ± 0.08	−0.01	1.15 ± 0.09	1.16 ± 0.08	+0.01
VE/VCO_2 slope	25.7 ± 4.2	25.6 ± 4.1	−0.1	26.0 ± 5.0	27.0 ± 4.3	+1.0	36.0 ± 4.3	34.8 ± 4.1	−0.6	34.1 ± 4.7	31.0 ± 4.3*†	−3.1†
Peak VD/VT	0.14 ± 0.02	0.15 ± 0.01	+0.01	0.14 ± 0.02	0.14 ± 0.01	0	0.20 ± 0.02	0.21 ± 0.01	+0.01	0.22 ± 0.03	0.19 ± 0.02*†	−0.03†
$\Delta VO_2/\Delta WR$ ($ml \cdot W^{-1} \cdot min^{-1}$)												
All exercise data	10.6 ± 3.0	10.6 ± 2.9	0	10.3 ± 2.4	10.5 ± 2.5	+0.2	7.8 ± 1.9	7.7 ± 1.9	−0.1	8.0 ± 1.7	9.2 ± 2.0*†	+1.2†
Below AT	9.2 ± 2.3	9.4 ± 2.1	+0.2	9.3 ± 2.2	9.1 ± 2.0	−0.2	5.8 ± 2.0	5.9 ± 2.1	+0.1	5.5 ± 1.8	8.4 ± 2.1*†	+2.9†
Above AT	10.8 ± 2.2	11.0 ± 2.1	+0.2	10.7 ± 2.0	10.6 ± 2.2	−0.1	8.5 ± 2.0	8.6 ± 2.0	+0.1	8.4 ± 2.0	10.6 ± 1.9*†	+2.2†
Tau recovery (s)	44.0 ± 16.0	44.7 ± 16.3	+0.7	45.2 ± 15.7	45.6 ± 15.5	+0.4	76.3 ± 13.1	76.5 ± 1.9	+0.2	76.7 ± 14.1	56.9 ± 12.8*†	−19.8†

*$p < 0.01$ vs. baseline; †$p < 0.01$ vs. placebo.
AT = anaerobic threshold; CHF = chronic heart failure; CPET = cardiopulmonary exercising testing; RER = respiratory exchange ratio; Tau = VO_2 time constant; VCO_2 = carbon dioxide production; VD/VT = dead space to tidal volume ratio; VE/VCO_2 slope = slope of increase in ventilation vs. carbon dioxide output; VO_2 = oxygen uptake; WR = work rate; Δ = changes from baseline.

Table 4. Brachial Artery Data at Baseline and After Placebo or Sildenafil Intake in Normal Subjects and in Patients With CHF (Mean ± SD)

	Normal Subjects						CHF Patients					
	Baseline	**Placebo**	**Δ**	**Baseline**	**Sildenafil**	**Δ**	**Baseline**	**Placebo**	**Δ**	**Baseline**	**Sildenafil**	**Δ**
Subjects (n)	8	8		8	8		16	16		16	16	
Flow-mediated changes in diameter (mm)	0.43 ± 0.04	0.44 ± 0.03	+0.01	0.43 ± 0.02	0.43 ± 0.04	0	0.25 ± 0.02	0.26 ± 0.03	+0.01	0.28 ± 0.03	0.36 ± 0.02*†	+0.08†
Reactive hyperemia ($ml \cdot min^{-1}$)	430 ± 35	432 ± 42	+2.0	428 ± 34	439 ± 38	+11.0	258 ± 47	253 ± 51	−5.0	261 ± 50	348 ± 61*†	+87†
Δ diameter/Δ flow ($mm \cdot ml^{-1} \cdot min^{-1} \cdot 1{,}000$)	0.99 ± 0.07	0.98 ± 0.06	−0.01	1.01 ± 0.08	0.97 ± 0.06	−0.04	0.87 ± 0.09	0.89 ± 0.07	+0.02	0.87 ± 0.13	1.04 ± 0.07*†	+0.17†

*$p < 0.01$ vs. baseline; †$p < 0.01$ vs. placebo.
CHF = chronic heart failure; Δ = differences from baseline.

Table 5. Pulmonary Function Data at Baseline and After Placebo or Sildenafil Intake in Normal Subjects and Patients with CHF (Mean ± SD)

	Normal Subjects					CHF Patients				
	Baseline	**Placebo**	**Δ**	**Sildenafil**	**Δ**	**Baseline**	**Placebo**	**Δ**	**Sildenafil**	**Δ**
Subjects (n)	8	8		8		16	16		16	
DLco ($ml \cdot min^{-1} \cdot mm\ Hg^{-1}$)	28.8 ± 3.9	27.2 ± 3.9	−1.6	27.9 ± 4.7	−0.9	21.5 ± 4.0	21.3 ± 3.6	−0.2	23.9 ± 4.0*†	+2.4†
DLco/V_A ($ml \cdot min^{-1} \cdot mm\ Hg^{-1}$)	5.5 ± 0.9	5.2 ± 0.7	−0.3	5.3 ± 0.8	−0.2	3.9 ± 0.6	3.8 ± 0.6	−0.1	4.7 ± 0.5*†	+0.8†
D_M ($ml \cdot min^{-1} \cdot mm\ Hg^{-1}$)	44.7 ± 2.8	45.1 ± 3.4	+0.4	44.3 ± 4.1	−0.4	30.3 ± 6.3	30.0 ± 4.9	−0.3	33.3 ± 5.0*†	+3.0†
D_M/V_A ($ml \cdot min^{-1} \cdot mm\ Hg^{-1}$)	8.6 ± 1.7	8.5 ± 2.1	−0.1	8.4 ± 1.3	−0.2	5.6 ± 1.2	5.5 ± 1.0	−0.1	6.7 ± 0.9*†	+1.1†
DLco/D_M ($ml \cdot min^{-1} \cdot mm\ Hg^{-1}$)	64.4 ± 5.3	60.3 ± 4.8	−3.1	62.8 ± 5.6	−1.6	70.2 ± 6.1	70.0 ± 5.0	−0.2	71.4 ± 5.3	+1.2
Arterial oxygen saturation (%)	98.3 ± 0.5	98.1 ± 0.4	−0.2	98.0 ± 0.5	−0.3	97.7 ± 0.7	97.9 ± 0.4	+0.2	98.1 ± 0.7	+0.4

*$p < 0.01$ vs. baseline; †$p < 0.01$ vs. placebo.
CHF = chronic heart failure; DLco = lung diffusion for carbon monoxide; D_M = alveolar-capillary membrane conductance; V_A = alveolar volume; Δ = changes from baseline.

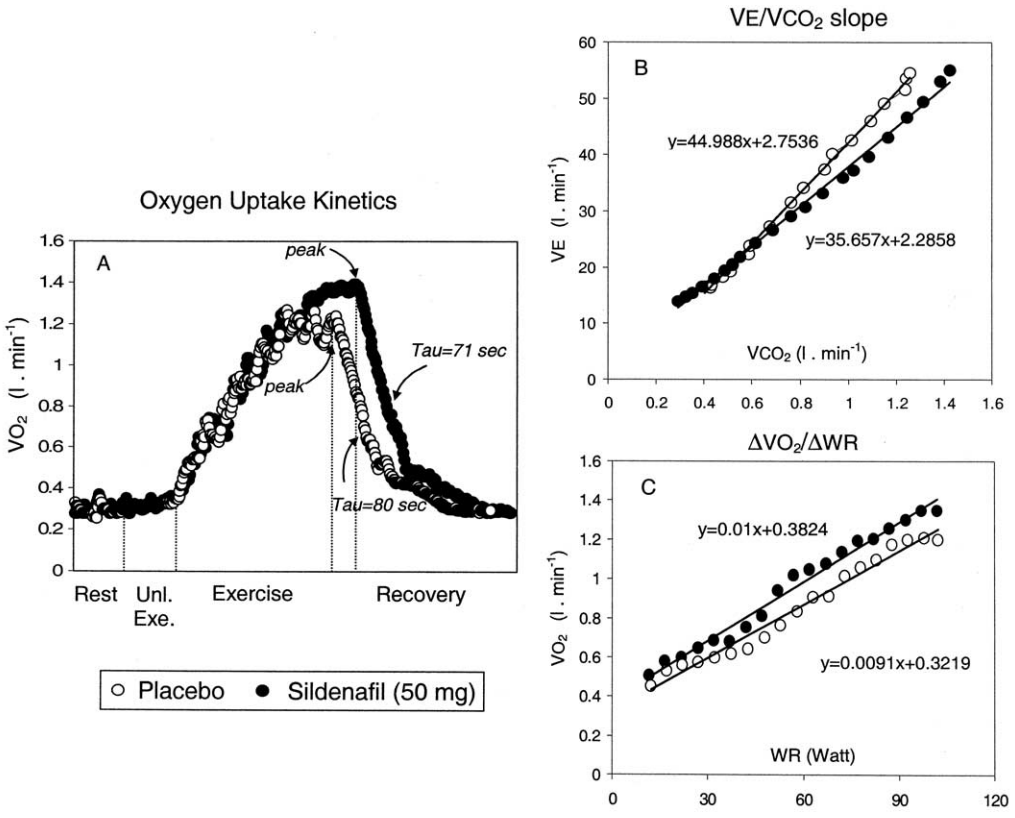

Figure 1. Cardiopulmonary exercising testing measurements (**A**, oxygen uptake [VO_2] kinetics; **B**, slope of increase in ventilation versus carbon dioxide production [VE/VCO_2 slope]; and **C**, rate of oxygen uptake increase per work rate [$\Delta VO_2/\Delta WR$]) of one patient with moderate congestive heart failure secondary to ischemic cardiomyopathy (age 60 years, left ventricular ejection fraction of 34%, and systolic pulmonary pressure of 38 mm Hg) recorded after placebo and after sildenafil intake. Protocol consisted of 2 min of rest, 2 min of unloaded exercise at 60 rpm (Unl. Exe.), ramp work rate of 15 $W \cdot min^{-1}$ to maximal exercise tolerance, and 6 min of recovery. Oxygen uptake kinetics data were computer-collected as breath-by-breath measurements, interpolated second-by-second, and averaged at 10-s intervals; VE/VCO_2 incremental changes during maximal exercise data are plotted at 20-s intervals; $\Delta VO_2/\Delta WR$ incremental changes during maximal exercise data are plotted at 20-s intervals.

ΔWR below AT rose from 5.5 ± 1.8 to 8.4 ± 2.1 ($p < 0.01$) and above the AT from 8.4 ± 2.0 to 10.6 ± 1.9 ($p < 0.01$), suggesting that an efficiency improvement occurred both below and above the AT. A consistent improvement in VO_2 kinetics was observed, as documented by a significant reduction in recovery tau from 76.7 ± 14.1 s to 56.9 ± 12.8 s. A representative case describing CPET changes during placebo and after sildenafil intake is reported in Figure 1. Peak VO_2 increased in 14 of 16 patients, and the VE/VCO_2 slope decreased in all patients.

The reduction from baseline in VE/VCO_2 slope with sildenafil was related to the increase in DLco ($r = -0.71$; $p = 0.0021$), and changes in $\Delta VO_2/\Delta WR$ were related to those in brachial reactive hyperemia ($r = 0.80$; $p = 0.0002$) (Fig. 2). A significant inverse relationship was found, both in the baseline and after sildenafil, of recovery tau with $\Delta VO_2/\Delta WR$ and with brachial reactive hyperemia (Fig. 3). There was no relationship between VE/VCO_2 slope and DLco at baseline or between brachial hyperemia and $\Delta VO_2/\Delta WR$ at baseline, as well as between age, etiology, and duration of heart failure and drug therapy, with changes in pulmonary artery pressure, arteriolar resistance, DLco, and D_M.

These effects were not detectable 24 h later at measurements performed in patients who were given placebo as second test drug. There were no major adverse effects attributable to the research procedures or to sildenafil. Minor adverse reactions to sildenafil administration consisted of flushing in three patients and in one healthy subject.

DISCUSSION

The novel findings are that, in CHF, PDE_5 inhibition attenuated secondary pulmonary hypertension by lowering arteriolar resistance, facilitated alveolar gas exchange, and improved overall exercise performance, VO_2 kinetics (recovery tau), and ventilation efficiency. In addition, sildenafil significantly improved the brachial artery flow-mediated endothelial function. These effects were not observed in control subjects.

Hemodynamics and alveolar gas diffusion. A previous study has prospected the possibility that sildenafil increases the ventricular contractile function (17). This, however, does not seem an appropriate explanation for changes observed in the pulmonary hemodynamics. In fact, as reported in other studies (18), wedge pulmonary pressure, cardiac output, and left ventricular ejection fraction were unchanged after sildenafil.

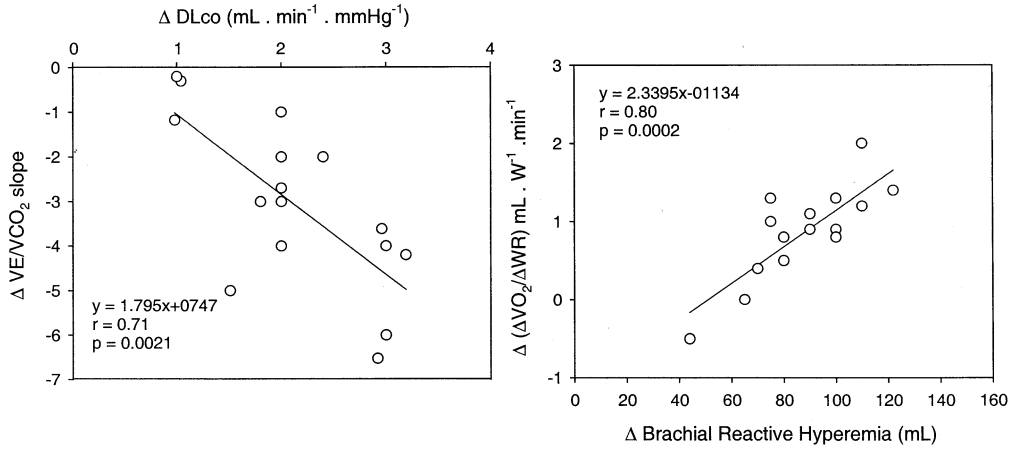

Figure 2. Correlations of changes, after sildenafil, in lung diffusing capacity for carbon monoxide (DLco) versus brachial artery reactive hyperemia and changes in slope of increase in ventilation versus carbon dioxide output (VE/VCO_2 slope) versus rate of oxygen uptake increase per work rate ($\Delta VO_2/\Delta WR$) in patients with chronic heart failure.

The basic mechanisms for secondary pulmonary hypertension in CHF are not entirely understood (19). Notably, in the present study, PDE_5 inhibition lowered arteriolar resistance in a vascular bed in which endothelium nitric oxide synthase is highly expressed (7) and in a clinical setting, heart failure, in which nitric oxide-mediated vasodilation is basically impaired (11). The interpretation that PDE_5 blockade lowers the pulmonary arteriolar resistance and pressure in patients with CHF by enhancing nitric oxide availability is consonant with these findings, as well as with the view that a defective nitric oxide release is typical of the syndrome and facilitates pulmonary vasoconstriction (19).

In anesthetized pigs, sildenafil administration augmented intrapulmonary shunt flow and lowered arterial O_2 saturation (17). These responses have been attributed to a vaso-

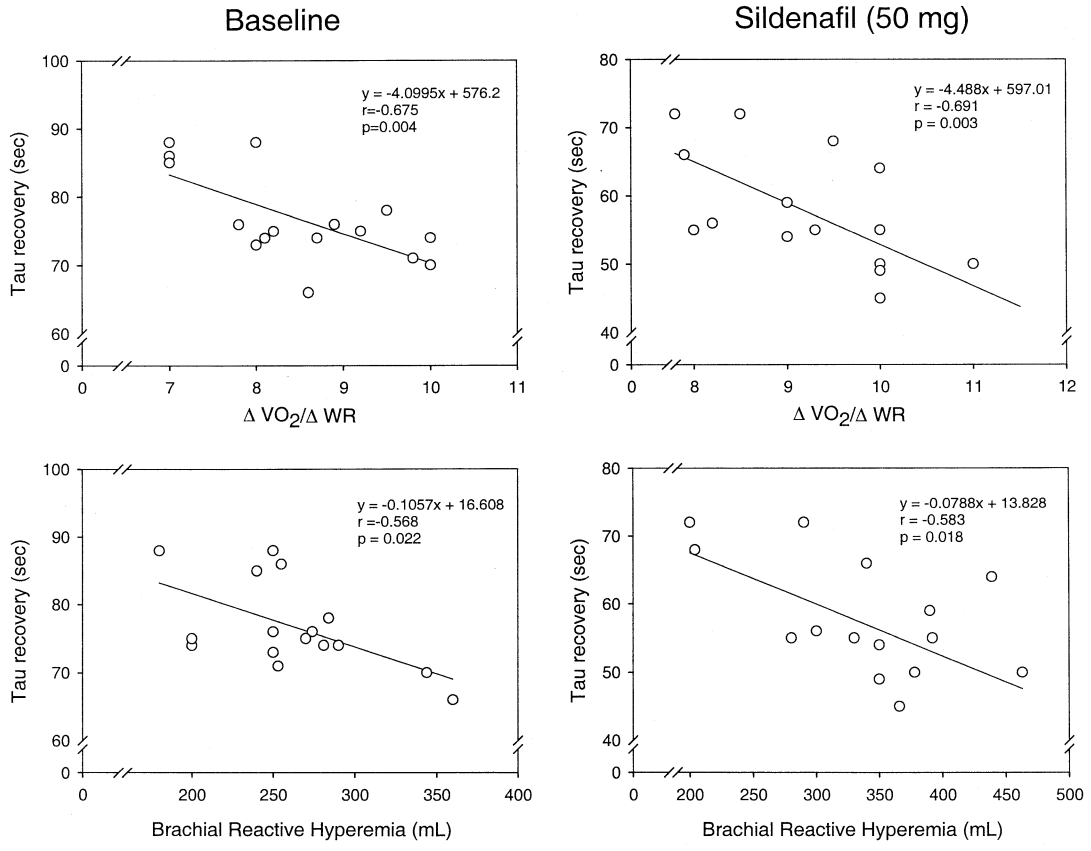

Figure 3. Correlations of changes in rate of oxygen uptake increase per work rate ($\Delta VO_2/\Delta WR$) versus tau recovery and brachial artery hyperemia versus tau recovery, at baseline and after sildenafil, in patients with chronic heart failure.

dilating effect and to a substantial increase in cardiac output that, in the presence of an unchanged ventilation, may have caused an inadequate gas exchange (17). Because of this, sildenafil effects on pulmonary hemodynamics and gas exchange might be undesired in patients with obstructive pulmonary disease (low ventilation/perfusion ratio) or with coronary disease (decrease in O_2 tension combined with an increase in cardiac output) (17). Our results are not consistent with increase in lung perfusion or with the occurrence of some arterial O_2 desaturation in normal subjects (18), as well as in patients with CHF when current doses of sildenafil are used. These drawbacks, therefore, would not preclude a possible use of the drug in patients with CHF.

Remarkably, PDE_5 inhibition promoted a very favorable reduction of the alveolar-capillary membrane resistance to gas exchange (improvement in D_M despite no changes in V_c). In CHF, elevation of hydrostatic forces, enhancement of sodium transport across the capillary endothelium, and reduction in active fluid reabsorption by alveolar epithelium (20,21) may concur to facilitate alveolar interstitial fluid accumulation and to limit gas exchange. Under this respect, a pertinent question is whether an improved DLco was related to the diminished pulmonary vascular tone, or to a direct effect mediated by the augmented nitric oxide availability, or both. How much of the benefit of sildenafil on gas transfer is due to a decrease of pulmonary vascular tone and pressure cannot be estimated. However, some considerations are in order. DLco increased because of a better alveolar membrane conductance, instead of an increased pulmonary capillary volume available for gas exchange (as would be expected if vasodilation were to be the mechanism). Hydralazine and nitrates (22) fail to improve DLco, despite a substantial pulmonary vasodilating activity. Insulin, on the contrary, in the absence of lung vasodilation (3), significantly improves conductance of the alveolar-capillary membrane, as well as exercise ventilatory efficiency, in patients with diabetes (23). Activation by insulin of the defective release of substances, such as endothelium-derived nitric oxide, has been offered as an explanation of these effects, because nitric oxide, like vasodilating prostaglandins (2,3), modulates the pulmonary vascular permeability and can reduce the tissue component of resistance to the O_2 transfer from the alveolus to its uptake by hemoglobin. These considerations may apply to sildenafil, mainly taking into account that lung function amelioration was paralleled by a substantial enhancement in the brachial artery endothelial function, and that a combination of a vascular and lung effect similar to this is also observed in CHF patients with exercise training (24), an efficacious stimulus for the release of endothelial paracrine agents. Thus, we propose the explanation of a greater nitric oxide availability as a mechanism for pulmonary vascular tone reduction and facilitation of gas diffusion after PDE_5 inhibition.

Exercise ventilation efficiency and VO_2 kinetics. Patients with CHF peculiarly exhibit an abnormal ventilatory response to exercise, characterized by a steep VE/VCO_2 slope. The increase in VE/VCO_2 slope may be multifactorial: increase of the ventilation required to overcome a large dead space, augmented central drive to ventilation originating from J-receptor activation in consequence of the interstitial space distension, bicarbonate buffering of accumulating lactic acid, reduced perfusion of ventilating lung, abnormal chemosensitivity, overactive ergoreceptors, abnormal autonomic and baroreceptor control of the circulation (25). In addition, in the presence of left ventricular dysfunction, exercise abnormally raises the pulmonary capillary pressure and the fluid flux transition. Thus, gas conductance may worsen because of an excessive fluid accumulation in the alveolar interstitium. Hyperventilation might help maintain O_2 alveolar tension at normal levels, at the price, however, of premature exhaustion of the ventilatory reserve and early exercise interruption. This study does not define the respective roles of these factors; however, the improvement in D_M, as possibly mediated by reduction of lung interstitial space overdistension and its correlation with the increased ventilatory efficiency (i.e., reduced VE/VCO_2 slope steepness), are in favor of an involvement of the membrane effects of PDE_5 inhibition. Likewise, the reduction of pulmonary dead space during exercise (decreased peak VD/VT) and the increase in $\Delta VO_2/\Delta WR$ (potentiated aerobic efficiency both below and above AT) are consistent with an influence of PDE_5 inhibition on more than one mechanism underlying the VE/VCO_2 slope improvement.

A better exercising muscle perfusion may also well explain the benefits of sildenafil on VO_2 AT, peak WR, and peak VO_2 (26). Nitric oxide has a physiologic role to dilate skeletal muscle vasculature, and this activity is impaired in several disorders including heart failure (9). The increase in $\Delta VO_2/\Delta WR$ reflects an increased quantity of O_2 utilized per unit increase in work rate and is a measure of aerobic efficiency. An improved O_2 diffusion from the capillaries to mitochondria or a facilitation of exercising muscle perfusion (changes in $\Delta VO_2/\Delta WR$ significantly correlated with variations in brachial artery reactive hyperemia with sildenafil) are factors potentially involved in the raised $\Delta VO_2/\Delta WR$. In our population, peak respiratory exchange ratio averaged 1.18 at baseline, and no changes were observed after sildenafil, suggesting a similar energetic substrate utilization. Consonant with these interpretations is the reduction in the recovery tau implying that O_2 debt accumulation, which is repaid after exercise, is mitigated by PDE_5 inhibition. Better correlations of recovery tau with $\Delta VO_2/\Delta WR$ and brachial artery dilation were observed after sildenafil intake.

These considerations, altogether, support the possibility that, in patients with CHF, impaired gas exchange efficiency is involved in the reduced peak VO_2, and that PDE_5 inhibition increases peak VO_2 and reduces exercise O_2 debt through a synergistic activity on central (lung) and peripheral (exercising muscle vasomotility) mechanisms.

Conclusions. In conclusion, this study provides novel information concerning the pathophysiology of CHF and the

effects produced by PDE_5 inhibition in this disease. It possesses the potential for future investigative and therapeutic developments.

Reprint requests and correspondence: Dr. Marco Guazzi, Cardiopulmonary Laboratory, University of Milano, Cardiology Division, San Paolo Hospital, Via A. di Rudini, 8, 20142 Milano, Italy. E-mail: Marco.Guazzi@unimi.it.

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